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Electronic Monitoring of Adherence, Treatment of Hypertension, and Blood Pressure Control

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BACKGROUND

Although it is generally acknowledged that electronic monitoring of adherence to treatment improves blood pressure (BP) control by increasing patients' awareness to their treatment, little information is available on the long-term effect of this intervention.

METHODS

In this observational study among a total of 470 patients with mild-to-moderate hypertension, adherence was measured in 228 patients by means of both the Medication Event Monitoring System (MEMS) and pill count (intervention group), and in 242 patients by means of pill count alone (control group). During a follow-up period of 1 year consisting of seven visits to the physician's office, BP measurements were performed and medication adjusted based on the achieved BP. In addition, at each visit adherence to treatment was assessed.

RESULTS

On the basis of pill counts, median adherence to treatment did not differ between the intervention group and the control group

(96.1% vs. 94.2%; $P = 0.97$). In both groups, systolic and diastolic BP decreased similarly: 23/13 vs. 22/12 mm Hg in the intervention and control group respectively. Drug changes and the number of drugs used were associated with BP at the start of study, but not with electronic monitoring.

CONCLUSIONS

In this study, electronic monitoring of adherence to treatment by means of MEMS did not lead to better long-term BP control nor did it result in less drug changes and drug use.

Keywords: adherence; blood pressure; compliance; electronic monitoring; hypertension

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Poor adherence to treatment remains one of the major limitations in the management of hypertension and may contribute to increased morbidity, mortality, and costs.¹⁻⁵ It is estimated that at least 50% of the patients with hypertension do not take antihypertensive medication as prescribed.⁶ Several large studies have shown that persistence with antihypertensive treatment decreases with time: discontinuation rates vary from 22% to almost 50% during the first year after initiation of therapy.⁷⁻¹⁰ Therefore, improving adherence to treatment remains a major challenge to the treating physician.

Electronic monitoring devices, such as the Medication Event Monitoring System (MEMS, Aardex, Zug, Switzerland), have

been used extensively in assessing adherence to antihypertensive drugs. The advantage of electronic monitoring is that a more detailed and accurate information is obtained than can be achieved with other methods.¹¹⁻¹⁴ In addition, electronic monitoring may improve adherence to treatment, as patients are aware of adherence monitoring. Hence, it may improve blood pressure (BP) control. Indeed, several studies have demonstrated a positive effect of electronic monitoring of adherence on BP control.¹⁵⁻¹⁹ However, most of these studies have followed patients for only a short period of time,¹⁵⁻¹⁸ making it difficult to predict how long the effect of electronic monitoring is sustained. Today, only one randomized study investigated the effect of electronic monitoring on long-term BP control.¹⁹ Patients whose drug intake was monitored had a greater decrease in BP than patients who received usual care. However, as adherence results were discussed with the patient it is not clear whether the greater reduction in BP is attributable to the electronic monitoring, the discussion with patients, or a combination of both.

Therefore, we investigated the effect of electronic monitoring of adherence to treatment, without discussing the results with the patients, on long-term BP control in patients with mild-to-moderate hypertension.

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METHODS

We performed an observational study in which all participating patients from the HOMERUS trial were included.^{20,21} In brief, HOMERUS is a multi-centre, prospective, randomized, double blind trial with a parallel-group design. Patients, aged 18 years and older whose office BP was above 139 mm Hg systolic and/or 89 mm Hg diastolic were recruited from the outpatient departments of four participating university hospitals and affiliated general practices. If the BP remained above 139/89 mm Hg at the second visit, patients were randomly allocated (minimization procedure) to either the self-pressure (SP) group or the office pressure group. If randomized to the SP group antihypertensive treatment was guided by the results of self BP measurement (SBPM). In the office pressure group, treatment was titrated on the basis of the office BP measurement. Both previously treated and untreated patients qualified for inclusion. In all of them, secondary hypertension had been ruled out by laboratory investigation. At entry into the study, any existing antihypertensive therapy was discontinued whenever possible and participants entered a placebo run-in period of 4 weeks duration before study treatment was initiated. Patients were followed-up for seven visits for a period of 1 year. After the third visit, patients were followed monthly; after the fifth visit patients were followed at a 2-months interval. The primary objective of the HOMERUS-study was to examine whether decisions concerning antihypertensive therapy based on SBPM could lead to less antihypertensive drugs used and associated costs, when compared to decisions based on office BP measurement. As a secondary objective, the effect of SBPM on adherence to medication within random subgroups of the SP and office pressure groups was investigated. For this secondary objective, adherence to treatment was electronically measured in all patients recruited by the coordinating centre (Maastricht University Hospital, Maastricht, The Netherlands) and surrounding general practitioners' practices. All patients gave their informed consent and the study was approved by the ethical committees of all participating centers before inclusion of patients into the study.

BP measurements. At every visit, three consecutive office BP measurements were performed in the hospital or at the general practitioners clinic. SBPM was performed six times a day (three in the morning and three in the evening) for a 7-day period, prior to every visit. Patients were requested to register their self-measurements on a form and to print out all measurements. Both office BP measurement and SBPM were always performed at the nondominant arm in sitting position after at least 5 min of rest, using the same fully automated device (Omron HEM-705 CP; Omron Healthcare, Kyoto, Japan).²²

Study treatment protocol. Treatment was instituted stepwise according to the following schedule:

Step 1: Lisinopril 10 mg once daily plus one tablet of placebo once daily;

Step 2: Lisinopril 20 mg once daily plus one tablet of placebo once daily;

Step 3: Lisinopril 20 mg once daily plus hydrochlorothiazide 12.5 mg;

Step 4: Lisinopril 20 mg once daily plus hydrochlorothiazide 12.5 mg plus amlodipine 5 mg.

In both the office pressure and SP group, the goal BP ranged between 120 and 139 mm Hg systolic and between 80 and 89 mm Hg diastolic. In patients who were above the target BP (systolic >139 mm Hg and/or diastolic >89 mm Hg), antihypertensive treatment was intensified by one step. If BP was lower than the target (systolic <120 mm Hg and diastolic <80 mm Hg), treatment was reduced by one step, eventually until termination of treatment. If patients were on their target, treatment remained unchanged. In case of refractory hypertension, defined as a sitting BP systolic >160 mm Hg or diastolic >100 mm Hg while the patient was already on the maximum combination therapy (i.e., step 4), additional strategies from other drug classes were instituted in order to further decrease BP level. Treatment decisions were taken at each visit and at the coordinating centre so that both the doctor and the patient were blinded for all study medication drugs. All drugs were prescribed to be taken in the morning and were supplied by the patient's own pharmacist.

Adherence measurements. In all patients pill counts were performed in order to calculate adherence rates. To minimize changes in patient's behavior, pill counts were done out of sight of the patient. In a sub-population of 228 patients, recruited by the coordinating centre (Maastricht University Hospital) and surrounding general practitioners' practices, drug intake was, in addition to pill counts, monitored electronically. Their adherence to antihypertensive medication was measured with MEMS V TrackCaps (Aardex), but without giving them feedback about their adherence behavior. The MEMS-TrackCap is an electronic monitoring system designed to compile the dosing histories of ambulatory patients who are prescribed oral medications.¹¹ Microelectronics integrated into the cap of pill containers record the time and date that the container is opened or closed.

Statistical analysis. Baseline characteristics were defined at enrollment of patients (visit 1), except for baseline BP which was determined at visit 3 after the placebo run-in period and before initiation of study treatment. The 228 patients from the centre in which drug intake was monitored both electronically and by pill count comprised the intervention group. The remaining patients originating from the other three centers at which only pill count was performed acted as controls. Although this study was an observational study nested in a randomized controlled trial, sample size calculations showed that at least 64 patients had to be included in both groups to detect a significant difference in change in BP between both groups. This calculation was based on a power of 80%, a significance level of <0.05, a minimal relevant difference in change in BP of 10 mm Hg, with a standard deviation of 20 mm Hg.¹⁵⁻¹⁹

Adherence measured by MEMS was expressed as "percentage of days with correct dosing"; a drug was considered to have

been taken correctly when the MEMS bottles were opened once every 24 h. Adherence measured by pill count was calculated as the percentage of the number of prescribed pills corrected for the number of returned pills divided by the period (in days) multiplied by 100%. Defined daily doses (DDD) of antihypertensive drugs were calculated according to data of the WHO Collaborating Centre for Drug Statistics Methodology.²³ DDDs are defined as 'the assumed average maintenance dose per day for a drug used for its main indication in adults.'²³ Antihypertensive drug modification was defined as an increase in drug dosage or adding in a new drug, or as a decrease in drug dosage or stopping a drug, or as a switch from one drug to another drug. Differences in adherence were analyzed as a continuous variable with the Mann–Whitney U test for non-normally distributed data. Differences in normally distributed continuous variables were analyzed with the Student's *t*-test. χ^2 tests were used to compare differences in categorical variables. Logistic regression models were fitted to assess the association of reaching target BP (<140/90 mm Hg) and allocated group adjusted for the following potential confounders: study centre, baseline BP, patient's age and sex, SP group, and DDDs. A *P* value smaller than 0.05 was considered to be statistically significant. Analyses were done on an intention-to-treat basis using SPSS version 15.0 (SPSS, Chicago, IL). The last observation carried forward method was applied for missing values when data of ≥ 2 consecutive visits were available.

RESULTS

In total, 510 patients met the inclusion criteria and were considered eligible for the study. Of these patients 40 withdrew or refused consent for various reasons. Consequently, 470 patients entered the study after a 4-week run-in period and started trial medication. Of these, 228 and 242 patients were categorized into the intervention and control group, respectively. Patients' baseline characteristics are presented in **Table 1**. Differences in baseline characteristics between the participating centers were significant for age, sex, and baseline office BP (both systolic and diastolic BP).

In the intervention group median adherence, expressed as days of correct dosing, was 91.6% (Inter Quartile Range 85.7–94.0%), whereas adherence according to pill count was 96.1% (Inter Quartile Range 88.8–98.4%) in this group. Patients in the intervention group showed an adherence determined by pill count which did not differ from controls (96.1% vs. 94.2%; *P* = 0.97). Based on pill count, median adherence in the total population to the antihypertensive drugs lisinopril, hydrochlorothiazide, amlodipine, and atenolol (i.e., the drugs that were prescribed according to the study protocol) was 93.1%, 95.3%, 94.9%, and 92.9%, respectively (*P* = 0.001).

Mean number of DDDs prescribed was higher in the intervention group than in the control group (2.3 vs. 1.9, *P* = 0.001). The number of DDDs prescribed for both groups increased throughout the study. For the periods between visit 7 to 8 (*P* = 0.025), 8 to 9 (*P* = 0.009), and 9 to 10 (*P* = 0.002) more DDDs were prescribed for patients in the intervention than in the control group. The number of DDDs was posi-

Table 1 | Baseline characteristics of the patients

Characteristic	Intervention (n = 228)	Control (n = 242)	<i>P</i> value
Age (years (s.d.))	57 (10)	54 (11)	<0.001
Male (n (%))	112 (49)	143 (59)	0.03
Smoking (n (%))	41 (18) ^c	41 (17)	0.43
Alcohol (n (%))	174 (76) ^b	190 (79) ^a	0.67
Body mass index (kg/m ² (s.d.))	27 (4)	28 (4)	0.64
Diabetes mellitus (n (%))	14 (6) ^c	10 (4)	0.43
SP group (n (%))	114 (50)	125 (52)	0.72
Baseline office blood pressure (mm Hg (s.d.))			
Systolic	169 (21)	160 (17)	<0.001
Diastolic	99 (11)	96 (10)	0.001
Number of patients on previous antihypertensive drugs (n (%))			
0	40 (18)	85 (35)	<0.001
1	86 (38)	91 (38)	0.98
2	74 (32)	46 (20)	<0.001
3 or more	28 (12)	19 (8)	0.11
Previous antihypertensive drugs (n (%))			
Diuretics	74 (32)	77 (32)	0.88
RAS inhibitors	118 (52)	81 (33)	<0.001
β -Blockers	83 (36)	61 (25)	0.0084
Calcium channel blockers	38 (17)	24 (10)	0.03
α -Blockers	4 (2)	5 (2)	0.81

Data are mean (s.d.) for continuous variables and number (%) for categorical variables. RAS, renin–angiotensin system; SP, self-pressure.

Data are missing for ^aone, ^btwo and ^cthree patients.

Table 2 | Number of drug additions or dose adjustments at the end of the follow-up period in the intervention and control group

Number of dose additions and/or increases	Number of patients with drugs addition and/or dose increase (n (%))		
	Intervention (n = 228)	Controls (n = 242)	RR ^a (95% CI)
–2	0 (0)	2 (0.8)	—
–1	12 (5)	14 (6)	0.91 (0.42–1.97)
0	25 (11)	46 (19)	0.58 (0.36–0.94)
1	30 (13)	47 (19)	0.68 (0.43–1.08)
2	50 (22)	34 (14)	1.56 (1.01–2.41)
≥ 3	111 (49)	95 (39)	1.24 (0.94–1.63)

CI, confidence interval; RR, relative risk.

^aAdjusted for systolic and diastolic blood pressure at baseline and self-pressure group.

tively associated with adherence to treatment determined by pill counts (*P* = 0.008), regardless of MEMS monitoring (*P* = 0.79). **Table 2** presents the number of drug additions or dose adjustments in both groups. Of the patients in the intervention group, 203 (89%) patients experienced one or more dose adjustments or drug additions compared to 196 (81%)

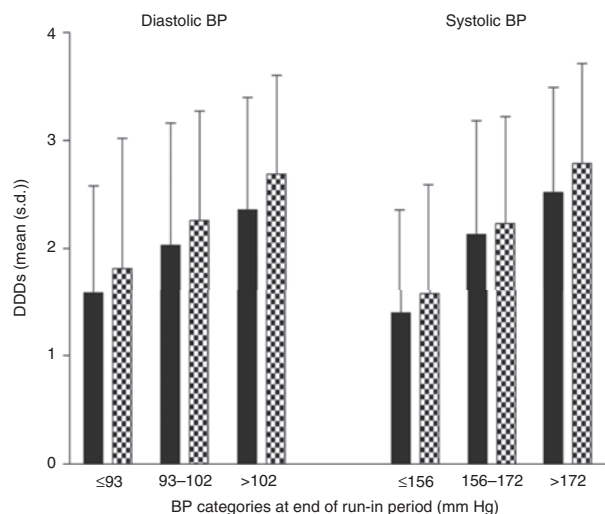


Figure 1 | Number of DDDs prescribed during the study based on categories of BP (systolic/diastolic) at baseline in the intervention (dotted bars) and control (black bars) group. BP, blood pressure; DDD, defined daily dose. *P* value for differences between intervention and control group >0.05 ; *P* value for DDDs at different BP values within intervention or control group <0.05 .

Table 3 | Blood pressure results after 12 months follow-up in intervention and control group

	Intervention (<i>n</i> = 228)	Controls (<i>n</i> = 242)	<i>P</i> value ^a
Achieved BP (mm Hg (s.d.))			
Systolic	146 (19)	141 (18)	0.001
Diastolic	86 (10)	85 (11)	0.002
Differences between initial and achieved BP (mm Hg (s.d.))			
Systolic	23 (23)	22 (19)	0.42
Diastolic	13 (13)	12 (11)	0.62

BP, blood pressure.

^aAdjusted for systolic and diastolic BP at baseline, age, and defined daily doses.

patients in the control group (adjusted odds ratio = 1.54; 95% confidence interval = 0.87–2.71). Patients who had a higher mean BP at baseline used more DDDs than patients who had a lower mean BP at baseline. This was observed in the intervention as well in the control group. Differences between groups were statistically not significant (Figure 1).

At the end of the study, patients in the intervention group reached a significant higher systolic and diastolic BP than patients in the control group (146/86 vs. 141/85 mm Hg, $P_{\text{adjusted}} = 0.001$ and $P_{\text{adjusted}} = 0.002$ for systolic and diastolic BP, respectively, Table 3). Figure 2 illustrates the time course of the office BP during the study. Systolic and diastolic BP increased after visit 1 when the run-in period started and the previous antihypertensive medications were discontinued. After visit 3, systolic and diastolic BP decreased in both groups. During that follow-up period, systolic and diastolic BP in the intervention group remained significantly higher than in the control group with the exception of visit 6 and 8 for diastolic BP. When we subtracted the achieved BP from the baseline BP, the net decrease

in systolic and diastolic BP was comparable in both groups (Table 3).

Over the 12-month period, less patients in the intervention group reached target BP ($<140/90$ mm Hg) when compared to patients in the control group: 90 (40%) vs. 131 (54%), $P = 0.001$. Monitoring was associated with an odds ratio = 0.55 (95% confidence interval = 0.38–0.80) for reaching BP control before adjustment, and an odds ratio = 0.44 (95% confidence interval = 0.28–0.69) after adjustment for study centre ($P = 0.012$), age ($P = 0.43$), female sex ($P = 0.002$), systolic ($P < 0.001$) and diastolic ($P = 0.004$) BP at baseline, and DDDs prescribed ($P = 0.98$).

DISCUSSION

The results from the present study suggest that BP is not better controlled in patients whose drug adherence is monitored electronically in addition to pill counts compared to those whose adherence is monitored by pill counts only. Therefore, these data do not support electronic monitoring of drug adherence as a useful tool to improve the management of hypertensive patients over a long period of time.

An effect of electronic monitoring on BP control may be a result of an increase in adherence to treatment in the intervention group. Although, we did not measure adherence electronically in the control group, we performed pill counts in both groups. Adherence according to pill counts was comparable in both groups. However, this result could be confounded by a difference in the number of DDDs prescribed between the intervention and control group. At the start of the HOMERUS trial, BP rates among patients in the intervention group were higher than in the control group. Consequently, the former used more DDDs for BP reduction. Although the number of DDDs was positively associated with adherence to treatment determined by pill counts, MEMS monitoring did not influence this association. These results may suggest that electronic monitoring by means of MEMS has no effect on adherence, resulting in comparable BP reduction rates in both groups.

In both the intervention and the control group we found a high median adherence according to pill counts of more than 94%. Moreover, our results showed that an increase in DDDs resulted in an increase in adherence. These observations could be a result of our study design in which patients had to attend many appointments with the physician in one year of follow-up. Recently, we have found that patients are more inclined to take their drugs as prescribed when they are faced with an upcoming consultation.²⁴ This phenomenon, also called white-coat compliance, underscores the importance of clinical visits for patients with hypertension. As a result, the absence of an effect of MEMS as an intervention on BP control and the high observed adherence may be explained by the frequent visits patients had to attend.

At this time, only two studies have investigated the effect of electronic monitoring of adherence to treatment on BP control in a randomized controlled setting.^{18,19} Wetzels and colleagues demonstrated that electronic monitoring reduces drug changes and drug use with BP control comparable to usual care.¹⁸ In

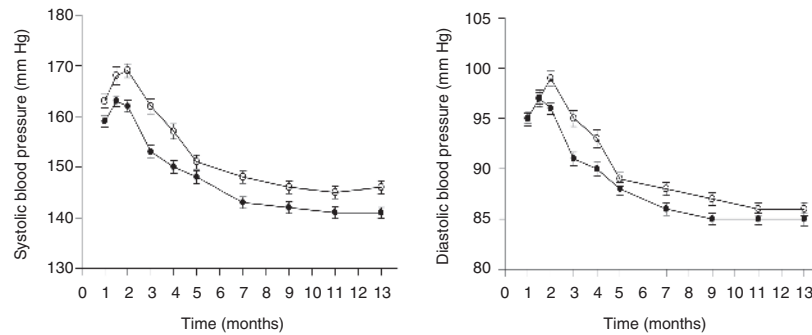


Figure 2 | Time course of systolic and diastolic blood pressure (BP) in the intervention (open circles) and control (closed circles) group. Differences in systolic BP between the intervention and control group are significant at all visits; differences in diastolic BP between the intervention and control group are significant at all visits, except at visit 1, 2, 6, and 8.

contrast, we did not find an indication that electronic monitoring was associated with less drug changes and drug use. In our study the number of DDDs used was based on the initial BP at baseline. Recently, Santschi and colleagues demonstrated that electronic monitoring led to better BP control, however the effect decreased over time.¹⁹ In that 12 months follow-up study, adherence rates were discussed with the patients, thereby possibly influencing the true effect of electronic monitoring on BP control. Given our results, the effect observed in Santschi's study may be attributable solely to the feedback provided by physicians to patients.

The results of our study must be interpreted within the context of its limitations. First of all, this study was not designed as a randomized controlled trial. In addition, the analysis was not powered to investigate differences between the intervention and control group. Adherence to treatment was measured electronically in a group of patients from the HOMERUS trial. The remaining population officiated as controls. Although, imbalances were observed in baseline characteristics between the intervention and control group, adjusting for these differences in a multivariate model had no effect on the association between electronic monitoring and BP control. It is therefore less likely that the study design influenced our results. Second, all patients in this study were aware that their adherence was being monitored, either by MEMS or by pill counts. In addition, patients had many appointments to attend with the physician within 1 year of follow-up. This may have resulted in a greater adherence than what is usually seen in the general population and, hence, overestimation of the habitual adherence of these subjects. Although, ideally, one would prefer not to inform patients that their adherence is being measured, ethical considerations preclude such an approach.

The extraordinary high adherence rate in the present study may complicate extrapolation of these results to the population at large. However, this high adherence rate does not necessarily imply that the study participants and/or their adherence behavior deviate from those in other studies. The two randomized studies performed by Wetzels and Santschi also showed adherence levels of more than 90%.^{18,19} In these studies the effect of electronic monitoring on BP reduction was only noticeable in the first months of the study. Several observational studies

showed that electronic monitoring significantly decreases BP. Despite comparable adherence levels between those studies and our study, the follow-up period was shorter when compared to our study (3–6 months vs. 12 months).^{15–17} Given our results and the long-term results observed by Santschi and colleagues,¹⁹ it is likely that an effect of electronic monitoring on BP diminishes when patients are followed for a longer period. It is however not known whether this effect is different in patients who are less adherent than patients in the described studies. Future studies should elucidate this.

Recently, we investigated whether deviant drug intake behavior occurred by comparing MEMS data and pill count data.²⁵ In that report we showed that deviant intake behavior occurred frequently but that this did not necessarily led to differences in BP control between groups. Consequently, we concluded that pill count could be a useful adjunct to MEMS caps for exploring deviant intake behavior. Furthermore, we stated that counting pills in adjunct to MEMS registration should be performed to identify true nonadherers. In the present study, we compared the 228 patients that were also included in the previous article with a population that did not participate in the previous study. The results of our previous paper and the present one can best be summarized as follows: today, none of the methods that are applied to monitor adherence to treatment is ideal and each has its specific shortcomings. Of the available methods MEMS seems to be the best, primarily because it provides hard data. Those hard data, however, refer only to the monitoring of the exact dates and times the patient is concerned with his or her medication. It does not give insight into the actual taking of the medication. Consequently, we previously recommended to combine MEMS with pill count. Nevertheless, whatever method one applies, it does not correlate very well with achieved BPs. This means that either all our methods, including MEMS, are fraught with error or there is more to reaching an acceptable BP level than adherence alone.

Taking our data together, our findings do not support the hypotheses that electronic monitoring by means of MEMS leads to better BP control or that it results in less drug changes and drug use. This may be due to the high overall adherence we have observed in our study as a consequence of the specific study design.

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